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Running Head: LVH in Atrial Fibrillation

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ABSTRACT

Left ventricular hypertrophy (LVH) is significantly related to adverse clinical outcomes in patients at high risk of cardiovascular events. Among atrial fibrillation (AF) patients, data on LVH, *i.e.* prevalence and determinants, are inconsistent mainly due to different definitions and to heterogeneity of study populations. We determined echocardiographic-based LVH prevalence and clinical factors independently associated with its development in a prospective cohort of non-valvular (NV) AF patients. From the ARAPACIS population, 1,184 NVAF patients (mean age 72±11 years; 56% male) with complete data to define LVH were selected. ARAPACIS is a multicenter, observational, prospective, longitudinal on-going study designed to estimate prevalence of peripheral artery disease in NVAF patients. We found a high prevalence of LVH (52%) in NVAF patients. When compared to those without LVH, AF patients with LVH were older and had a higher prevalence of hypertension, diabetes and previous myocardial infarction (MI). A higher prevalence of ankle-brachial index (ABI) ≤0.90 was seen in LVH patients (22 vs. 17%, p=0.0392). LVH patients were at significantly higher thromboembolic risk, with CHA_2DS_2-VASc ≥2 seen in 93% of LVH and in 73% of non-LVH patients (p<0.05). Women with LVH had a higher prevalence of concentric hypertrophy than men (46% vs. 29%, p=0.0003). Logistic regression analysis demonstrated that female sex (odds ratio (OR): 2.80, p<0.0001), age (OR: 1.03 per year, p<0.001), hypertension (OR: 2.30, p<0.001), diabetes (OR: 1.62, p=0.004) and previous MI (OR: 1.96, p=0.001) were independently associated with LVH.

In conclusion, NVAF patients have a high prevalence of LVH, which is related to female sex, older age, hypertension and prior MI. These patients are at high thromboembolic risk and deserve a holistic approach to cardiovascular prevention.

KEY WORDS: atrial fibrillation, left ventricular hypertrophy, sex, ischemic stroke risk.

Atrial Fibrillation (AF) is the most prevalent supraventricular tachyarrhythmia [1,2] associated with high risk of death and stroke [3]. Hypertension is the most frequent cardiovascular risk factor in AF and recognized as a predictor of new onset AF [4-6]. One of the hypertension-related target organ damage is left ventricular hypertrophy (LVH) [7-10]. Data on sex differences in development of LVH have been reported in hypertensive patients with [11] or without concomitant heart failure [10]. Notwithstanding different definitions and threshold criteria, LVH prevalence ranges widely in the general population [10]. Nonetheless, LVH is an independent risk factor for major cardiovascular events and all cause death [12-15]. Also, left ventricular remodeling has been identified as an independent risk factor for stroke and mortality in AF patients [16]. The aim of our study was to determine LVH prevalence, using well-defined echocardiographic criteria based on left ventricular mass (LVM) indexed by body surface area (BSA) in a cohort of non-valvular (NV) AF patients. Secondly, we aimed to identify the clinical factors independently associated with LVH in our patients with NVAF. Third, we conducted a sex-stratified analysis to investigate relevant sex differences in LVH in NVAF patients.

METHODS

We performed a cross-sectional analysis on the "Atrial Fibrillation Registry for Ankle-brachial Index Prevalence Assessment: Collaborative Italian Study" (ARAPACIS) a multicenter, observational, prospective on-going study designed to estimate prevalence of Ankle-brachial index (ABI) ≤0.90 in NVAF patients and its influence on cardiovascular and cerebro-vascular events incidence over a 3 year-follow up. [17,18].

Details on standard study procedures have been previously reported [18]. In addition, a standard trans-thoracic echocardiography (TTE) [19] was performed where feasible. Even if a central analysis of echocardiographic images wasn't performed, an experienced cardiologist in

echocardiography performed a blinded evaluation of measurements for consistency and reliability.

Patients were consecutively recruited, both as in- or out-patients, if they were ≥18 years old and had NVAF diagnosis recorded in the preceding 12 months. Enrollment was performed in 136 facilities belonging to the Italian Internal Medicine Society (SIMI) network from October 2010 and continued until 30 October 2012. All patients signed a written informed consent. The study was conducted in accordance with the EU Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

Left ventricular mass (LVM) estimation was calculated according to American Society of Echocardiography (ASE) and European Association of Echocardiography (EAE) joint recommendations [19]. LVM values have been indexed by body-surface area (BSA), calculated with the Dubois and Dubois formula (BSA = 0.007184 x weight $[Kg]^{0.425}$ x height $[cm]^{0.725}$). Thus, we defined the presence of LVH for a LVM indexed by BSA (LVMI-BSA) > 95 g/m^2 for women and an LVMI-BSA > 115 g/m^2 for men [19].

The definition of LV remodeling was assessed calculating the relative wall thickness (RWT). In accordance to ASE/EAE recommendations [19], RWT ≥ 0.42 defined a concentric remodeling, otherwise a RWT <0.42 defined an eccentric remodeling. All patients were then categorized into 4 categories of cardiac remodeling: (I) No Remodeling, i.e. patients without LVH and with a RWT < 0.42; (II) Concentric Remodeling, i.e. patients without LVH and with a RWT ≥ 0.42; (III) Eccentric Hypertrophy, i.e. patients with LVH and a RWT < 0.42; and (IV) Concentric Hypertrophy, i.e. patients with LVH and a RWT ≥ 0.42.

According to Shapiro-Wilk normality test, variables with a normal distribution were tested for differences by Student t test and reported as mean±SD. Variables with non-homogeneous variances were tested by Mann Whitney U test and reported as median and interquartile range

(IQR). Categorical variables, expressed as counts and percentages, were analyzed by a chi-square test. A sex-stratified analysis was also conducted. Finally, a multivariate regression analysis was performed in order to establish LVH determinants in NVAF patients. To reduce inter-observer variability, the regression analysis was corrected for enrolling centers. The probability values were 2-sided; a p value <0.05 was considered statistically significant. All analyses were carried out with SPSS v.20 (IBM, NY, USA).

RESULTS

Among a total of 2,027 patients enrolled in ARAPACIS, echocardiographic data were available in 1,184 subjects (59%). After data revision, 1,087 patients (72±11 years; 56% male) were eligible for analysis (Figure 1). Clinical and demographic variables in non-included patients were similar to those analyzed (Table 1).

Previous cardiovascular disease (CVD) was recorded for about a quarter of patients. Among classical cardiovascular risk factors, hypertension was the most prevalent (82%). The mean LVMI-BSA was 112±31 g/m^2. Values of LVMI-BSA were higher in permanent NVAF compared to those with persistent AF (p=0.0107) or paroxysmal AF (p=0.0023). LVMI-BSA progressively increased with higher CHA_2DS_2-VASc risk classes (p<0.0001) [Figure 2].

LVH was recorded in 52% of patients. Clinical and demographic characteristics among the groups are reported in Table 1. LVH patients were older, had a higher prevalence of hypertension, diabetes and previous myocardial infarction (MI) compared to those without. ABI≤0.90 was prevalent in LVH patients. CHA_2DS_2-VASc ≥2 class was recorded more frequently in LVH patients.

Table 2 summarizes echocardiographic characteristics of the 2 groups. LVH patients had poorer ventricular function when compared to non-LVH ones. In 59% of LVH patients there was a Concentric Hypertrophy pattern.

Pharmacologic treatments distribution in the 2 groups, are reported in Table 3. LVH patients were more likely treated with oral anticoagulants (OAC) and angiotensin-converting enzyme inhibitors (ACEI) than non-LVH ones.

Final forward logistic model showed that female sex (Odds Ratio [OR]: 2.808, 95% Confidence Interval [CI]: 2.152 – 3.664, p<0.001), age (OR per year: 1.035, 95% CI: 1.021 – 1.048, p<0.001), hypertension (OR: 2.302, 95% CI: 1.606 – 3.299, p<0.001), diabetes (OR: 1.623, 95% CI: 1.169 – 2.253, p=0.004) and previous MI (OR: 1.964, 95% CI: 1.328 – 2.903, p=0.001) were independently associated with LVH. No influence of enrolling centers was evident.

LVH was detected in 67% of NVAF women compared to 42% in men. Number of atherosclerotic risk factors was higher in male patients with LVH compared to those without (2.04±1.20 vs. 1.76±1.02, p=0.0041). Similar data were recorded in LVH female patients compared to non-LVH ones (1.92±1.12 vs. 1.70±1.10, p=0.0434). Concentric Hypertrophy was more common in female patients (F=46% vs. M=29%, p=0.0003). Women with LVH, compared with men, were less treated with OAC (65% vs. 69%, p=0.0318).

DISCUSSION

The present analysis of a selected cohort from the ARAPACIS study provides, for the first time, data on the high prevalence of LVH, defined as LVM indexed by BSA. Second, we identified female sex, age, hypertension, diabetes and previous MI as clinical factors associated with the presence of LVH among NVAF patients. Third, we observed that concentric hypertrophy was the most common remodeling pattern in female NVAF patients.

These findings could contribute to a better understanding of ventricular remodeling among patients with NVAF. In fact, previous clinical studies reported a huge range (from 23% to 68%) of LVH prevalence in AF [15,16], probably due to heterogeneity of patients enrolled or to different LVH evaluations [15,16]. Using a standard recommended method for LVH definition, we have now

provided more reliable data on LVH prevalence among NVAF patients. Second, taking in account that LVMI-BSA seems to be one of the most reliable method to determine the cardiovascular risk associated with left ventricular remodeling [20], our work could represent a premise for evaluating clinical usefulness of LVH detection in cardiovascular risk assessment also in NVAF patients. Indeed, higher prevalence of ABI≤0.90 could suggest an association between atherosclerosis and LVH [21,22], which requires further investigations. Moreover, the recognition of LVH may play a pivotal role to correctly stratify cerebrovascular risk of NVAF patients as reported in hypertensive patients [23,24]. In fact previous data demonstrated that increased LVM, as well as abnormal RWT, are associated with increased risk of stroke in hypertensive patients, even higher in patients with a concentric pattern [24].

A post-hoc analysis from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial [16] reported that LVH assessed by LVM was an independent predictor of both all-cause mortality and stroke among AF patients [16]. Further evaluations of follow up data of ARAPACIS study will provide a relevant evidence to clarify this poorly explored issue.

Although LVH patients are at higher thromboembolic risk, we found suboptimal OAC use, as previously reported for the overall ARAPACIS study population [17]. Moreover, female LVH patients seem to be significantly less treated with OAC. Considering the higher stroke risk in women with LVH when compared to men with or without LVH [25,26], the underuse of OAC could contribute to the higher stroke risk of female patients. The standard evaluation of LVH presence in NVAF patients could be useful to better define thromboembolic risk, independently by other thromboembolism risk factors. When available, prospective data coming from ARAPACIS study might clarify this aspect.

Our data suggest that different LVH development among sex might be relevant in stratifying thromboembolic risks of NVAF patients. The prevalence of concentric hypertrophy in our NVAF female patients was significantly higher comparing with men. Indeed, experimental data suggest that cardiac hypertrophy development in response to a pathological stimulus may be blunted in women compared with men [27], yet the relative mortality risk, when hypertrophy does occur, is greater in women and is more commonly concentric [28,29]. As stated above, concentric hypertrophy among hypertensive patients carries the greatest stroke risk [24]. Furthermore, sex differences in LVH distribution and worse cardiac remodeling in NVAF patients may partly explain why female gender confers additional risk of thromboembolic stroke. Accordingly, the presence of LVH, as defined by electrocardiography, confers a higher stroke risk of in LVH AF patients [15].

As with any observational analysis, residual unmeasured confounders may exist and impact the validity of our results. Given the cross-sectional nature of the study, data presented cannot establish a pathophysiological link between NVAF and LVH, but provide hypothesis-generating associations. Given that hypertension was highly prevalent amongst NVAF patients, and since hypertension represents a fundamental risk factor for the developing of LVH, we cannot establish whether LVH was evident prior to the development of NVAF. Lastly, the present analysis is based on the assumption that walls thickness and geometry are homogenous. This assumption could bias the evaluation of LVH prevalence, even if reduced by the use of three different measurements to assess LVM.

To summarize, NVAF patients have a high prevalence of LVH, which is related to female sex, older age, hypertension and prior MI. Ongoing prospective data from the ARAPACIS study will clarify the potential predictive role of LVH among NVAF patients.

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FIGURES LEGEND

Figure 1. Flow diagram NVAF patient selection

LVH= left Ventricular Hypertrophy; NVAF= Non-Valvular Atrial Fibrillation.

Figure 2. LVMI-BSA values distribution according to CHA_2DS_2-VASc score*

LVMI-BSA= Left Ventricular Mass indexed by Body Surface Area; NVAF= Non-Valvular Atrial Fibrillation.

TABLE 1: CLINICAL AND DEMOGRAPHIC CHARACTERISTICS ACCORDING TO THE PRESENCE OF LEFT VENTRICULAR HYPERTROPHY

Variable	Excluded Patients	Left Ventricular Hypertrophy		*P value*
		Yes	No	*Yes vs. No*
	N= 940	N=576	N=511	
Age (years.), mean±SD	74±9	75±9	70±12	<0.0001‡
Age Classes				<0.0001¤
<65 years	263 (28%)	123 (21%)	191 (37%)	
65-74 years	209 (22%)	141 (25%)	142 (28%)	
≥75 years	468 (50%)	312 (54%)	178 (35%)	
Women	439 (47%)	353 (56%)	158 (31%)	<0.0001¤
Body Mass Index (Kg/m^2), mean±SD	28±5	28±5	28±5	0.4876‡
Type of Atrial Fibrillation				0.0866¤
Paroxysmal	425 (45%)	233 (41%)	221 (43%)	
Persistent	120 (13%)	82 (14%)	90 (18%)	
Permanent	395 (42%)	261 (45%)	200 (39%)	
Hypertension*	785 (84%)	515 (89%)	374 (73%)	<0.0001¤
Diabetes Mellitus	237 (25%)	152 (26%)	77 (15%)	<0.0001¤
Smoker	138 (15%)	77 (13%)	100 (20%)	0.0057¤
Hypercholesterolemia#	353 (38%)	231 (40%)	205 (40%)	0.9964¤
Metabolic Syndrome	282 (31%)	164 (30%)	141 (29%)	0.6767¤
Previous Transient Ischemic Attack/Stroke	116 (12%)	67 (12%)	52 (10%)	0.4429¤
Previous Myocardial Infarction	159 (17%)	105 (18%)	49 (9.6%)	<0.0001¤
Previous Peripheral Artery Disease	13 (1.4%)	9 (1.4%)	10 (1.9%)	0.5624¤
Heart Failure	189 (20%)	102 (18%)	87 (17%)	0.7668¤
Ankle-Brachial Index ≤0.90¶	212 (23%)	128 (22%)	88 (17%)	0.0391¤
CHA_2DS_2-VASc, median [IQR]	3 [2-4]	4 [3-5]	2 [1-4]	<0.0001§
CHA_2DS_2-VASc Classes				<0.0001¤
Score 0	25 (2.7%)	8 (1.4%)	46 (9.0%)	
Score 1	108 (11.5%)	35 (6.1%)	94 (18.4%)	
Score≥2	807 (85.8%)	533 (92.5%)	371 (72.6%)	

Legend: IQR= Interquartile Range; SD= Standard Deviation.
*Blood Pressure>140/90 mmHg or treated with anti-hypertensive drugs; #Total Cholesterol≥ 240 mg/dL or treated with lipid lowering drugs; ¶ Data referred to 1,084 patients; ‡ Student t test; ¤ χ^2 test; § Mann Whitney U test.

TABLE 2: ECHOCARDIOGRAPHIC CHARACTERISTICS ACCORDING TO THE PRESENCE OF LEFT VENTRICULAR HYPERTROPHY.

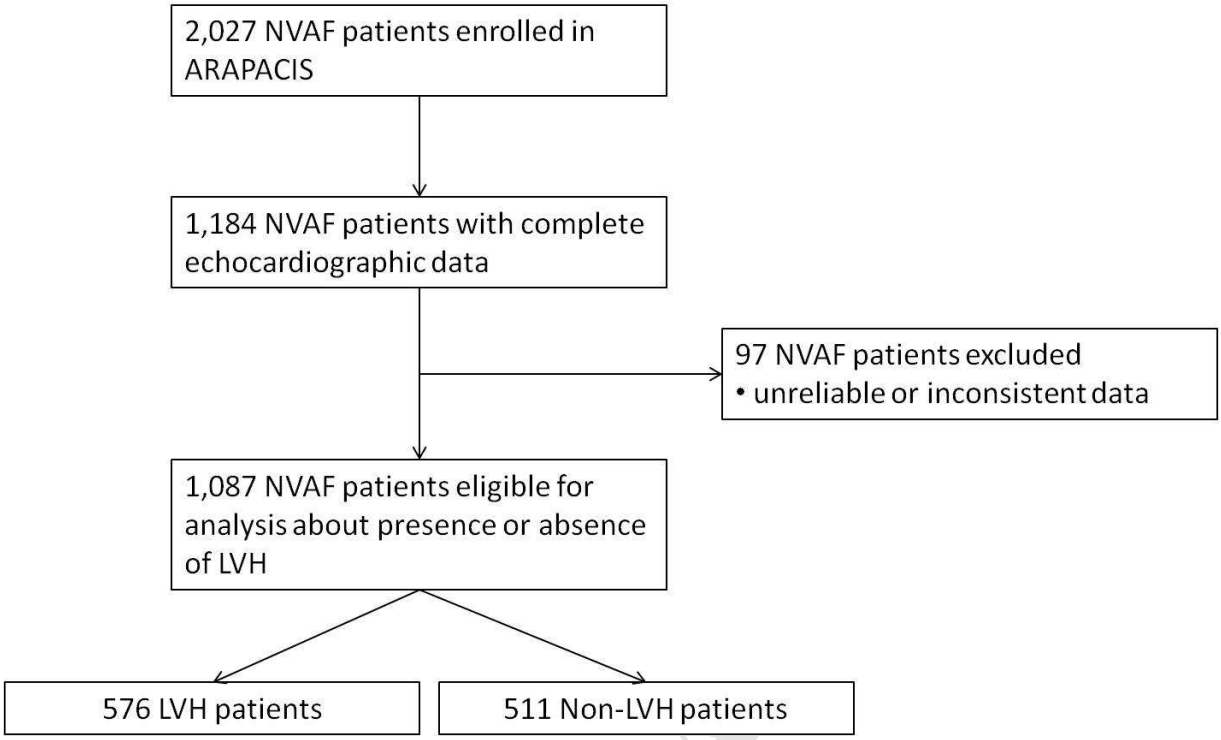
Variable	Left Ventricular Hypertrophy		*p*
	Yes N=576	No N=511	
Left Ventricular Ejection Fraction (%), mean±SD	54±10	57±8	<0.0001‡
Left Ventricular Ejection Fraction <50%	133 (23%)	62 (12%)	<0.0001¤
Left Ventricular Mass Indexed by Body Surface Area (g/m^2), mean±SD	132±27	89±15	<0.0001‡
Relative Wall Thickness (>0.42)	338 (59%)	215 (42%)	<0.0001¤
Left Ventricular Internal End-Diastolic Dimension (mm), mean±SD	53±6	48±5	<0.0001‡
Interventricular Septum Thickness (mm), mean±SD	12±2	10±2	<0.0001‡
Posterior Wall Thickness (mm), mean±SD	11±2	9±1	<0.0001‡
Left Atrial Diameter (mm), mean±SD¶	45±8	44±9	0.2488‡
Cardiac Remodeling			<0.0001¤
None Remodeling	0 (0)	296 (58%)	
Concentric Remodeling	0 (0)	215 (42%)	
Eccentric Hypertrophy	238 (41%)	0 (0)	
Concentric Hypertrophy	338 (59%)	0 (0)	

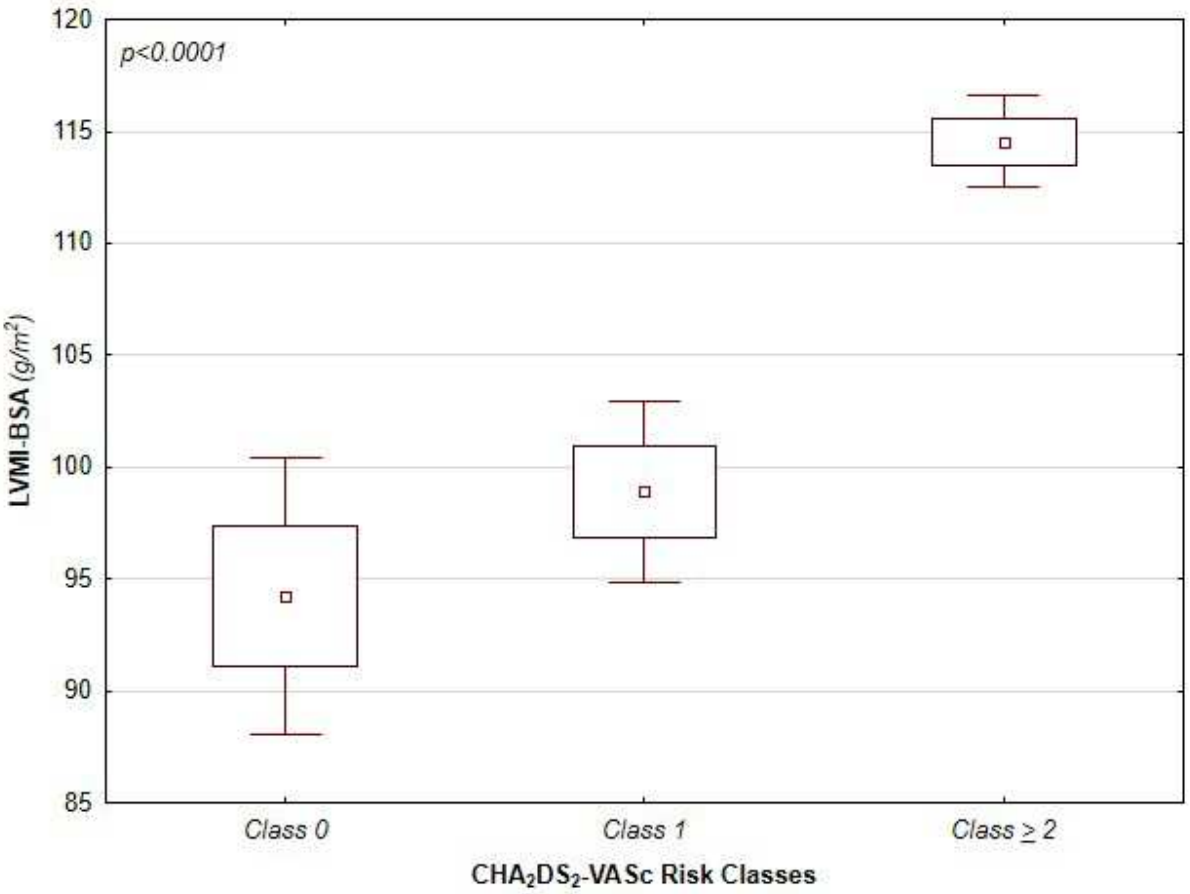
Legend: SD= Standard Deviation.
¶ Data referred to 912 patients; ‡ Student t test; ¤ χ^2 test.

TABLE 3: PHARMACOLOGIC TREATMENTS DISTRIBUTION ACCORDING TO THE PRESENCE OF LEFT VENTRICULAR HYPERTROPHY-

Variable	Left Ventricular Hypertrophy		
	LVH N=576	Non-LVH N=511	*p¤*
Anti-Thrombotic			0.0134
None	48 (8.3%)	62 (12%)	
Oral Anticoagulant	381 (66%)	309 (61%)	
Antiplatelets	117 (20%)	125 (25%)	
Oral Anticoagulant+Antiplatelets	30 (5.1%)	15 (2.9%)	
Statins	218 (38%)	189 (37%)	0.7697
Beta-Blockers	260 (45%)	213 (42%)	0.2513
Angiotensin-Converting-Enzyme Inhibitors	222 (39%)	155 (30%)	0.0045
Angiotensin II Receptor Blockers	212 (37%)	169 (33%)	0.1979
Calcium Channel Blockers	165 (29%)	127 (25%)	0.1591
Nitrates	83 (14%)	38 (7.4%)	0.0002
Antiarrhythmics	159 (28%)	156 (31%)	0.2888
Digoxin	117 (20%)	64 (13%)	0.0005
Diuretics¶	293 (60%)	193 (45%)	<0.0001
Oral Hypoglycemic Agents	92 (16%)	52 (10%)	0.0049
Subcutaneous Insulin	44 (7.6%)	11 (2.1%)	<0.0001

Legend: ¶ Data referred to 859 patients; ¤ χ^2 test.




p<0.0001
120
115
110
105
100
95
90
85
LVMI-BSA (g/m²)
Class 0
Class 1
Class ≥ 2
CHA₂DS₂-VASc Risk Classes

APPENDIX

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